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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,416	07/27/2006	Johan Axelman	PU0404	7278

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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,416	AXELMAN ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Preliminary amendment to claims 1-24 filed on 07/27/06 is acknowledged.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-17 and 24, drawn to a method for reducing total sample complexity.

Group II, claim(s) 18-23, drawn to a system for reducing total sample complexity.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the common technical feature for the inventions is a mass spectrometer, since separation in he method can be performed by 2D electrophoresis, rather than by chromatography. This is not a special technical feature, and therefore the restriction is proper.

3. During a telephone conversation with Younggaug Ji on 06/12/09 a provisional election was made without traverse to prosecute the invention of Group I , claims 1-17 and 24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 18-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-17 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The pending claims are directed toward the method for reducing total sample complexity in native or digested biological samples without any indication, as to which samples these are. The specification discloses specifically application of the method to proteomes, i.e. to protein analysis and to digested protein samples which comprise a mixture of polypeptides. The specification does not provide any disclosure for any pother type of biological samples.

The examiner respectfully reminds the Applicants that according to MPEP §2163:

> **"2163.02. Standard for Determining Compliance with Written Description Requirement:**
>
> The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention.

> See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

The Applicants did not reasonably convey to a person skilled in the art that they possessed the invention in the scope of the present claims at the time the application was filed, since they did not provide such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-17 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites in the preamble "the method for reducing total sample complexity ... before analysis by mass spectrometry", while the body of the claim recites the step of MS analysis. The examiner suggests changing the preamble of the claim to "the method of mass spectrometric analysis of native or digested biological samples comprising proteins by reducing total sample complexity" or something like that.

From the claims it is not clear, as to which samples besides proteins can be digested, especially in the light of several dependent claims. The examiner considers the term "biological samples" in the context of claim 1 unclear and indefinite.

Claim 8 is unclear, as it is not apparent, as to whether it is a three-dimensional chromatography which is recited in the claim. Also, it is not apparent, as to why MS/MS is considered to be a part of the separation step b), rather than the step of analysis c) of the parent claim.

From claims 13 and 24 it is unclear, as to how the method can be integrated to a conventional MDLC flow path.

Claim Rejections - 35 USC § 102/103

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. **Claims 1-2, 8-9, 11-17 and 24** are rejected under 35 U.S.C. 102(b) as being anticipated by, or, in the alternative, under 35 U.S.C. 103(a) as obvious over the prior art disclosed in Millea et al. (J. Chromatogr., A, 2005) (all references are prior to 2003) (PA Millea).

PA Millea teaches the following:

> "Multidimensional separations that utilize orthogonal separation mechanisms offer improved separation capabilities over single dimension separations, and allow an increased number of components to be detected from complex mixtures. The basic

theories on multidimensional separations provide that the resultant peak capacity of a two-dimensional (2D) separation can approach the product of the peak capacities of the individual dimensions [18–20]. The realization of this capacity requires the pairing of dimensions with sufficient selectivity differences to make efficient use of the increased separation space.

Wide variety of multidimensional separation mechanisms have been coupled together to resolve complex protein mixtures, often in combination with on-line or off-line mass spectrometry. Chromatofocusing [6,21,22], size-exclusion [4,23,24], affinity [25], and ion-exchange chromatography [26,27] have all been used as a first dimension separation in combination with RPLC for online MS analysis of proteins. **Free-flow electrophoretic–isoelectric focusing coupled with non-porous RPLC and ESI-TOF-MS detection has been used to examine the proteome of a human erythroleukemia cell line byWall et al. [28,29].** Liu et al. [26], applied an integrated strong cation-exchange/reversed-phase (SCX/RPLC) 2D system with online MS detection to characterize yeast ribosomal extracts. Size-exclusion chromatography (SEC) followed by RPLC and MS detection was described by Nemeth-Cawley et al. [11]. In this study, the accurate mass determination of intact proteins using a quadrupole time-of-flight (Q-TOF) MS system permitted determination of component heterogeneity within an immunoglobulin fusion protein. Opiteck et al. have employed comprehensive multidimensional separations using both SEC/RPLC [30] and SCX/RPLC [31] systems combined with mass spectrometry for the characterization of intact proteins within an Escherichia coli cell lysate. These works illustrate the effectiveness of coupling multiple liquid phase separations with MS detection for the in depth characterization of protein samples." (Page 288, left column).

Thus disclosure covers possible variations of multidimensional chromatography including the one, in which the first separation occurs via anion exchange chromatography, with several possible variations for the second separation in the second dimension, which makes the subject matter of the indicated claims either anticipated or obvious over the prior art disclosed by Millea.

Claim Rejections - 35 USC § 103

13. The text of those sections of Title 35, U.S. Code not included in this paragraph can be found in the previous paragraph.

14. **Claims 3 and 7** is rejected under 35 U.S.C. 103(a) as being unpatentable over PA Millea.

Since the separation based on pI-value is the purpose of applying multidimensional chromatography as disclosed in the PA Millea, selecting an optimal pI range for more efficient MS analysis would have been obvious for a routineer on the art.

15. **Claims 5, 6, 9 and 10** are rejected under 35 U.S.C. 103(a) as being unpatentable over PA Millea in view of Tsonev et al. (US 2007/0144973)(Tsonev).

PA Millea does not specifically teach an embodiment, in which the cation exchange chromatography is coupled with anion exchange chromatography, with the separation first taken place on anion chromatographic column, followed by cationic chromatography.

Tsonev teaches:

"[0058] In another aspect of the invention, there is provided a combined external gradient chromatofocusing method of chromatographically separating charged molecules having different isoelectric points, comprising:

[0059] applying the charged molecules to be separated to an anion exchange adsorbent, which is followed by a cation exchange adsorbent connected in series such that the two adsorbents are perfused with a solvent comprising at least one buffering component at an initial pH, where each of the charged molecules to be separated fall into one of three charge classes: negatively charged for those charged molecules that have apparent pIs below the initial pH; neutral for those charged molecules that fail to bind to either the anion exchange adsorbent or the cation exchange adsorbent at the initial pH; and positively charged for those charged molecules that have apparent pIs above the initial pH;

[0060] binding the charged molecules which are negatively charged at the initial pH to the anion adsorbent;

[0061] binding the charged molecules which are positively charged at the initial pH to the cation adsorbent;

[0062] collecting those charged molecules which fail to bind to either the cation exchange adsorbent or the anion exchange adsorbent at the initial pH;

[0063] disconnecting the anion exchange adsorbent and the cation exchange adsorbent from each other at the initial pH;

[0064] supplying to the anion exchange adsorbent an eluent with a time dependent decreasing pH starting at the initial pH formed from the continuous mixing of a solution at the initial pH containing the at least one buffering component pumped out from a first reservoir with a solution at a different pH containing the at least one buffering component pumped out from a second reservoir, wherein the mixing proportions vary to maintain an unretained pH gradient with an externally defined slope;

[0065] collecting the charged molecules, each of which separately elutes from the anion exchange adsorbent at its effective isoelectric point, until a final minimum pH is reached;
[0066] supplying to the cation exchange adsorbent an eluent with a time dependent increasing pH starting at the initial pH formed from the continuous mixing of a solution at the initial pH containing the at least one buffering component pumped out from a first reservoir with a solution at a different pH containing the at least one buffering component pumped out from a second reservoir, wherein the mixing proportions vary to maintain an unretained pH gradient with an externally defined slope; and
[0067] collecting the charged molecules, each of which separately elutes from the cation exchange adsorbent at its effective isoelectric point until a final maximum pH is reached" (Pages 3-4).

It would have been obvious for a person of ordinary skill in the art to modify the method disclosed in PA Millea by applying a combination of anion-cation exchange chromatography the way it as disclosed by Tsonev, because such modification provides much better and more controllable separation of the proteins and/or peptides for further MS analysis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Y. Kim can be reached on (571) 272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797

6/22/2009